REMARKS

Applicants respectfully request reconsideration and allowance of the claims, as amended, in light of the remarks made herein.

Claims 1-23 and 27-40 are under examination in this application. Claims 1-4, 23, 27, 35 and 40 have been amended. Support for each amendment can be found throughout the specification and from the claims as filed. Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

The amendments are introduced to address the Examiner's specific concerns and to more particularly point out and distinctly define the subject matter Applicants regard as the invention. No new matter has been added.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited by the Examiner, and that these claims were in full compliance with the requirements of 35 U.S.C. §112. The amendments of and additions to the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled. Furthermore, it is explicitly stated that the herewith amendments should not give rise to any estoppel, as the herewith amendments are not narrowing amendments.

Oath/Declaration

A new oath or declaration was required by the Office Action. An executed declaration has not been received from the inventors, but will be forwarded in a separate Communication upon its receipt by the undersigned.

The Rejection Under §101 Is Overcome

Claims 1-23 and 27-40 were rejected under 35 U.S.C. §101 because the claims allegedly recite products of nature. Claims 1-4, 35 and 40 have been amended, as suggested by the Examiner, to refer to the "hand" of the inventor. The rejection is traversed with respect to the remaining claims.

Claims 7-23 recite compositions, formulations or medicaments. The "hand of man" is inherently involved in these embodiments, and therefore, no amendment is necessary. *See In re Bergstrom*, 166 USPQ 150 (CCPA 1970). Further, claim 27 already recites an organism "in

substantially pure form" and claims 30 and 31 refer to a "biologically pure culture". Therefore, reconsideration and withdrawal of the §101 rejection are requested.

The Rejections Under §112 Are Overcome

Claims 1-23 and 27-40 were rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. The Office Action stated that the claimed *S. salivarius* strains must be available to the public.

With respect to these biological materials, the undersigned states that she is a registered patent attorney representing the Applicants, that the biological materials, accession no. DSM 13084 and DSM 13085, identified in the application as deposited, were deposited under the terms of the Budapest Treaty with Deutsche Sammlung für Mikroorganismen und Zellkulturen (DSMZ), having an address at Mascheroder Weg 1b, D-38124 Braunschweig, Germany, and that:

(a) during the pendency of this application, access to each of the Deposits will be afforded to the Commissioner upon request;

(b) all restrictions upon availability of the each of the Deposits to the public will be irrevocably removed upon granting of the patent;

(c) each of the Deposits will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer;

(d) a test of the viability of the biological material at the time of each of the Deposits was made; and

(e) each of the Deposits will be replaced if it should ever become inviable.

The Office Action further states that claims to variants of SEQ ID NO:3 would involve undue experimentation to determine which amino acids should be inserted, deleted or substituted. Applicants disagree. The claims refer to variants having greater than 80% amino acid sequence homology with the protein of claim 1 or claim 2.

Variant proteins with an amino acid sequence greater than 80% homologous with the amino acid sequence of the native Salivaricin B are disclosed at page 6, lines 10-11 of the description as filed. One to three amino acid insertions, deletions, or substitutions are particularly contemplated in claim 4. Such modified versions of the claimed protein are fully disclosed at page 6, lines 13-28 of the description as filed. Further, as noted at page 7, lines 4-7

of the description as filed, variants or modified versions of the protein may be made by techniques which are well known to those skilled in the art. It is therefore submitted that the particularities of the claimed variants and modified versions of the Salivaricin proteins are disclosed and described. Applicants are not required to exemplify every variant of a fully described species, such as the antibacterial Salivaricin protein exemplified in the application. It is well within the ability of those of ordinary skill in the art to make and recognize the claimed variants or modified proteins based on the sequence and activity, without undue experimentation. It is further submitted that the Applicants are entitled to the scope of the claims and should not be unreasonably deprived of the benefits of their invention by others making minor variants or modifications to the disclosed amino acid sequences.

The Office Action further objects that the claims are overly broad and speculative. Applicants disagree and point out that equivalent proteins can be obtained from other S. salivarius strains and other streptococcus. More particularly, once the Applicants have identified the new Salivaricin protein described in the application, and its molecular weight, amino acid sequence, encoding nucleotide sequence, and function, one of ordinary skill in the art can readily identify other organisms producing the clearly defined protein. One of ordinary skill in the art is also enabled, by the teachings of the description as filed, to prepare recombinant organisms by standard conventional techniques which are capable of expressing the described Salivaricin protein. Again, the Applicant would be unfairly deprived of the benefits of the invention should the claims be limited in the manner suggested by the Office Action. Others would be able to engineer, in a routine manner, a wide range of organisms capable of expressing the Salivaricin protein. Such methods are well known and are described at pages 9 and 10 of the specification as filed.

Claims 1-23 and 27-40 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. The amendment to claim 1 clarifies that SEQ ID NO:1 represents the N-terminal amino acid sequence of the claimed protein and that it is isolated from the microorganism.

With respect to claims 21 and 22, the rejection is traversed. The Salivaricin B protein claimed is the primary antibacterial agent. The protein can be present in the formulation on its own. Claim 21 therefore specifies that the formulation may further comprise one or more secondary antibacterial agents. In claim 22 it is specified that the second antibacterial agent is

selected from BLIS. Therefore it is clear that what is claimed is an additional BLIS in the formulation. Also comprehended is the situation where the S. salivarius strains K12 and K30 express both Salivaricin B and Salivaricin A2. Inclusion of both BLIS is said to render the formulation particularly bacteriocidal (see for example, page 16, last paragraph).

In view of these arguments and amendments, reconsideration and withdrawal of the rejections under §112 are solicited.

The Rejection Under §102 Is Overcome

Claims 1-15, 21-23 and 27-40 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Caufield et al. The rejection is traversed. The Office Action has identified the Caufield reference as publishing SEQ ID NO:3. The Office Action does not identify which of the sequences in Caufield has 87% amino acid identity to the claimed SEQ ID NO:3. Our initial analysis suggests that the Examiner is looking at SEQ ID NO:8 which, as noted in the Office Action, differs by four amino acids over the 25 amino acid sequence, i.e.

Tagg SEQ ID NO:3	1 GGGVIQTISHECRMNSWQFLFTCCS 25
Caufield SEQ ID NO:8 (lacticin 481)	27 GSGVIHTISHECNMNSWQFVFTCCS 51

Our analysis suggests that this gives 84% homology, rather than the 87% recited by the Office Action. However, there is an important point to note regarding the comparison of the peptide sequences of Salivaricin A and that of Caufield's lacticin (SEQ ID NO:8), which is that the propeptides (biologically active parts of the molecules after leader cleavages) actually differ by a further two amino acids from that shown in the 25 amino acid sequences. As depicted in Figure 7 of Caufield, the sequence for LcnDrl prolantibiotic (SEQ ID NO:8) is in fact:

KGGSGVIHTISHECNMNSWQFVFTCCS

If a direct comparison of the propeptides is carried out, then there are in fact six amino acids different between the sequences giving a percentage homology of 77.56%, which is less than 80% limit identified in the claims. There are also significant differences in the leader sequences of the two molecules if a full comparison of the sequences is carried out.

Lacticin 481 is mentioned in the background of the specification at page 1, line 24. As noted there, it is derived from Lactobacillus lactis, not from Streptococcus salivarius. The Applicants have also cross-tested the Salivaricin B and Lacticin 481 producer strains and have

demonstrated that Salivaricin B producers kill the Lacticin 481 producer strain (i.e. Lacticin 481 immunity mechanism does not protect against the cell B). By contrast, the Lacticin 481 producer does not kill the Salivaricin B producer strain (i.e. Salivaricin B immunity mechanism does protect against Lacticin 481),

The Caufield protein therefore has a different sequence, is derived from a different organism, and has a different functionality. The Applicant therefore submits that the specific S. salivarius antibacterial proteins with their identified bacteriocidal properties and requirement for greater than 80% homology with the protein isolated from S. salivarius strain K12 are not anticipated by the Caufield sequence.

Reconsideration and withdrawal of the §102 rejection are requested.

The Rejection Under §103 Is Overcome

Claims 1-11, 13, 21-23 and 27-40 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by or, in the alternative, under 35 U.S.C. §103(a) as allegedly obvious over Ross et al., Tagg, Sanders et al., Matsushiro or Kawai et al. The rejection is traversed.

The Ross publication discloses Salivaricin A from Streptococcus salivarius 20P3. As noted in the background to the specification, while Salivaricin A demonstrated inhibitory activity against a number of streptococcal species, the activity was bacteriostatic rather than bacteriocidal. Salivaricin A, and microorganisms producing it, therefore do not provide a complete answer for controlling streptococcal infection. In contrast, Salivaricin B, which is claimed in the instant application, has been identified as bacteriocidal, as opposed to being simply bacteriostatic.

The cited Tagg article teaches S. salivarius having a high instance of BLIS production, particularly of Salivaricin A. No disclosure is made of the specifically claimed Salivaricin B protein, nor is it suggested in the article that any of the Salivarius strains identified produce Salivaricin B.

The Sanders document teaches the production of the antibiotic Enocin from S, salivarius strain K58. The antibiotic is stated to inhibit group A streptococci, including Streptococcus pyogenes. Enocin is a very small molecule (less than 200 Da, as estimated by Sephadex G25 chromatography). It appears to be a competitive inhibitor of pantothenate uptake by bacteria such as S. pyogenes, that are unable to synthesize their own pantothenic acid. Enocin is

therefore also bacteriostatic not bacteriocidal (see column 1, lines 64-66), and differs significantly from the lantibiotic Salivaricin B presently claimed.

Matsushiro teaches lactic acid producing strains of S. salivarius which have the ability to degrade dental plaque. There is no suggestion that the Matsushiro strains produce the presently claimed Salivaricin B protein, nor any suggestion that the strains are bacteriocidal, particularly against Streptococcus pyogenes, There is simply no motivation in this patent to produce the presently claimed proteins, organisms, and formulations.

Kawai also teaches various stains of streptococcus bacteria which can be used to deliver lactic acid bacteria to the intestine of a person who needs same. There is again no teaching of Salivaricin B or its properties, nor would it be obvious to produce same based on teachings in this document. Prior to the teachings of the instant application, it was not recognized that a bacteriocidal lantibiotic was being produced from S. salivarius, and accordingly, it would not have been obvious to isolated or purify proteins from the organisms disclosed in these references.

It is possible that the Examiner may be misinterpreting the statement at page 4, last paragraph, as meaning the all S. salivarius will produce the claimed BLIS. This is not in fact the case. A review of the Tagg paper above indicates that of the 1450 strains of S. salivarius, 45 are BLIS producing strains, and at that time 12 different types of BLIS were identified as being produced. It is therefore clear that only a low percentage of S. salivarius actually produce BLIS, and the number and effect of those BLIS may vary.

It is neither taught nor suggested by any of the documents in question that Salivaricin B is produced by any of these organisms, that it is active against Streptococcus pyogenes, and that it is a bacteriocidal strain as opposed to a bacteriostatic strain.

Moreover, because the Salivaricin B protein is novel and inventive, all of the protein and formulation claims, organisms, and method of treatment claims which produce or use Salivaricin B are similarly novel and inventive over and above the teachings of Caufield alone, or taken together with the secondary documents cited.

CONCLUSION

No fee is believed to be due for entry and consideration of this paper, however, the Commissioner is authorized to charge any fee occasioned by this paper, or credit any overpayment of such fees, to Deposit Account No. 50-0320.

Applicants take this opportunity to thank the Examiner for acknowledging Applicants' claim for priority under 35 U.S.C.§ 119 and receipt of the copies of the certified copies of the priority documents.

In view of the remarks and amendments herewith, the application is in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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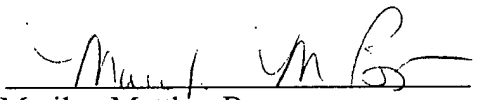
By: 
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims

1. (Amended) An isolated antibacterial protein [which can be] isolated from *S. salivarius* strain K12 on deposit at Deutsche Sammlung von Mikroorganismen Und Zellkulturen GmbH, Braunschweig, Germany, accession number DSM 13084, which has a molecular mass of approximately 2733 Da. as determined by ion-spray mass spectrometry, and the N-terminal amino acid sequence represented by[of] SEQ ID NO: 1, or an antibacterial fragment or variant thereof which variant has greater than 80% amino acid sequence homology with said protein.

2. (Amended) An isolated antibacterial protein having the amino acid sequence of SEQ ID NO: 3 or an antibacterial fragment or variant thereof, which variant has greater than 80% amino acid sequence homology with said protein.

3. (Amended) An isolated antibacterial protein having the amino acid sequence of SEQ ID NO: 3.

4. (Amended) An isolated antibacterial protein which has an amino acid sequence which differs from the sequence of SEQ ID N0 3 by the insertion, deletion or substitution of from one to three amino acids.

23. (Amended) A therapeutic formulation as claimed in claim 20 which includes one or both of Salivaricin A, an organism which can express Salivaricin A, the antibacterial protein which has the amino acid sequence of SEQ ID NO:5,[as defined in claim 41] or an organism which can express the antibacterial protein which has the amino acid sequence of SEQ ID NO:5[as defined in claim 41].

27. (Amended) An organism, in substantially pure form, which includes a polynucleotide which:

a) encodes a protein as claimed in any one of claims 1-6;

b) comprises the coding sequence of SEQ ID NO:2; or

c) encodes a protein as claimed in any one of claims 1-6, comprising the DNA sequence which encodes an antibacterial protein as claimed in claim 1, which is part of the genome of S. salivarius strain K12, on deposit at Deutsche Sammlung von Mikroorganismen Und Zellkulturen GmbH, Braunschweig, Germany, accession number DSM 13084[as claimed in any one of claims 24-26 and is capable of expressing an antibacterial protein as claimed in any one of claims 1-6].

35. (Amended) A method as claimed in claim 33 wherein said inhibitory effect is caused by colonising at least part of the upper respiratory tract of an individual with a viable organism in substantially pure form which expresses said protein.

40. (Amended) A method of treatment of a patient against infections of the upper respiratory tract caused by streptococcal organisms which comprises the steps of:

(i) orally administering to said patient an amount of an antibiotic effective to reduce the numbers of streptocci present; and

(ii) administering, to the resulting bacterially depopulated environment, *S. salivarius* organism(s) in substantially pure form which produce BLIS to repopulate said environment.

ABSTRACT OF THE DISCLOSURE

This invention provides an antibacterial protein, Salivaricin B. Salivaricin B is bacteriocidal with respect to, *inter alia, S. pyogenes* and therefore has numerous therapeutic applications. These applications include, but are not limited to, forming part of therapeutic formulations for use in treating or preventing streptococcal infections of the throat.